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Brain tumor research in the UK: current perspective and future challenges

A strategy document from the NCRI brain tumor CSG

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Abstract

The National Cancer Research Institute (NCRI) is a partnership of charity and government research funders whose purpose is to improve health and quality of life by accelerating progress in cancer-related research through collaboration. Under this umbrella, the NCRI Brain Tumor Clinical Studies Group is focused on improving clinical outcomes for adult patients with brain and central nervous system tumors, including those with brain metastasis from other primary sites. This document discusses the current state of clinical brain tumor research in the UK and the challenges to increasing study and trial opportunities for patients. The clinical research priorities are defined along with a strategy to strengthen the existing brain tumor research network, improve access to tissue and imaging and to develop the future leadership for brain tumor research in the UK. This strategy document may serve as a framework for other organizations and countries.

Introduction

The National Cancer Research Institute (NCRI) partnership was established in 2001 to ensure collaboration and coordination amongst cancer research funders in order to maximize the value and benefits of cancer research for patients and the public. Within the NCRI, clinical studies groups (CSGs) were established across the major cancer sites to provide a forum for stakeholders to develop trials and build a strategic portfolio within their areas of expertise. The original remit of the CSGs was to promote trials within the clinical community and also to provide constructive support for study proposals prior to submission to funding agencies. More recently the remit has changed and CSGs are now expected to be more active in developing clinical trials in-house, with particular emphasis on interventional rather than observational studies.

Since its formation the brain tumor CSG has been supported by subgroups; namely (i) Translational and Novel Agents, (ii) Imaging and Technology [originally separate groups which merged in 2012] and (iii) Supportive and Palliative Care. These subgroups provided a crosscutting approach to studies across all brain tumor types. Pediatric brain tumors fall under the remit of the Children's Cancer and Leukaemia CSG and due to the age eligibility criteria for most clinical trials, the groups function largely independently. Over the last decade the number of trials on the NCRI portfolio has increased. Neurosurgeons have developed and led both surgical trials such as GALA-5 ¹ and GALA-BIDD ² and radiotherapy trials such as the ROAM trial (an international multi-center phase III trial for atypical meningioma) ³. Imaging trials such as DIG PRaM-GBM have been developed and led by neuroradiologists and neurosurgeons. Similar success has been achieved by oncologists who have taken laboratory research in DNA damage and repair biology into clinical trials for patients with gliomas, in the form of the PARADIGM ⁴ and OPARATIC trials ⁵.

Despite these successes, feedback from the NCRI highlighted that by their nature only a limited number of patients were eligible for these trials. Targeting therapeutics in stratified patient cohorts is likely to exacerbate this trend, and such trends are exacerbated in less common cancers such as those of the brain. There is a need to balance how we can achieve large-scale research involving patients across the whole of the UK and addressing all aspects of the cancer journey.

The NCRI brain tumor CSG held a strategy meeting at Peterhouse College, Cambridge on 10-11th October 2016. Members of the CSG and subgroups, along with representatives from The Brain Tumor Charity, braintrust – the brain cancer people, Cancer Research UK (CRUK), the Department of Health and the National Institute of Health Research (NIHR) discussed the current state of brain tumor research in the UK and its future challenges. This document summarizes those discussions and outlines a forward strategy for clinical brain tumor research in the UK.

Burden of disease

Approximately 9000 patients are diagnosed with a primary brain tumor each year in the UK, and it has been estimated that 16,000 patients suffer from brain metastasis from other primary sites making a total of approximately 25,000 patients affected per year in the UK ⁶. Over 102,000 people are living with a brain tumor in the UK ⁷ and overall, only 14% of patients with primary brain cancer are alive 10 years after diagnosis ⁶. Although there are approximately 120 different types of brain tumor, the most common are gliomas, meningioma and metastases from extra-cranial sites such as breast, lung, kidney and skin. Glioblastoma is the commonest primary malignant brain tumor and the cause of the greatest average loss of life-years among all cancers ⁸ with a 2 year survival of ~25% and 5 year survival of ~5%.⁹

Meningiomas, meanwhile, are the commonest primary intracranial tumor overall. The majority can be cured by surgical resection but in a subset of patients with clinically aggressive meningioma the tumor may recur. Radiotherapy may also help control these tumors, but there are no effective chemotherapy treatments¹⁰. Furthermore, cure or disease control does not necessarily equate to maintained quality of life and patients can often suffer a great deal of morbidity due to the location of the meningioma and the post treatment effects.

Brain metastases affect up to 40%¹¹ of patients with an extracranial primary cancer, with an increasing incidence because of both more effective control of the primary tumor and greater use of brain imaging for detection of metastasis. Surgery, stereotactic radiosurgery and whole brain radiotherapy continue to be the mainstay of treatment but increasingly therapies are targeted according to primary tumor type, including molecular subtype. Although some patients undoubtedly benefit from these targeted therapies, the overall prognosis for brain metastases is generally poor, and there are few effective treatments that can achieve long-term control^{11,12}.

Although the incidence, care pathways and specialists involved vary according to primary and secondary brain tumours, all types have a major impact on patients and carers, since they directly affect personality, mood, speech, physical function, cognitive function, seizure threshold, and levels of fatigue. As such, common themes emerge regardless of tumor type, for example, the primary effect of the tumor and the destructive or toxic side effects of the treatment (surgery, radiotherapy, and chemotherapy). Accordingly quality of life is a major issue for patients living with and beyond brain cancer. Taken together there is an urgent need both to improve brain tumor survival, and to improve the quality of life for those who do live longer and have additional morbidity from treatment.

Stakeholders in brain tumor research

Patients with brain tumors can suffer from a range of neurological and quality of life issues that require coordinated management by a large multi-disciplinary team (MDT). NICE Guidance on “improving outcomes for people with brain and other CNS tumors” (<https://www.nice.org.uk/guidance/csg10>) identifies key MDT members including neurosurgeons, neurologists, neuropathologists, neuroradiologists, oncologists, clinical nurse specialists, and Allied Health Professionals. Many different professions and organisations therefore contribute to and are integral to brain tumor research. There is strong backing within this community to fund and support research that will directly benefit patients, families and carers. As well as Cancer Research UK (CRUK), charities specifically dedicated to brain cancer research, include The Brain Tumor Charity (TBTC), Brain Tumor Research (BTR) and brainstrust – the brain cancer people. These charities have their own unique approach to brain cancer research – for example, brainstrust is a patient facing support charity and focuses on clinical research to improve patient and caregiver quality of life. The Brain Tumor Research charity is very active at lobbying for additional government funding as well as fundraising for several University BTR centers of excellence. The Brain Tumour Charity raises money to fund research through programme and project grants. Despite these differences they all identify brain cancer as a priority area and nurturing this broad community of stakeholders is central to improving outcomes for patients living with brain tumors.

Funding landscape: lessons from other cancers

Two types of cancer demonstrate clearly the positive long-term correlation between research investment and survival rates; namely breast cancer and leukemia, which account for 8.5% and 6.9% of all NCRI spending, respectively (www.ncri.org.uk). Breast cancer

survival after 5 years is now as high as 84.3%, despite more than 50,000 new cases being diagnosed every year. This remarkable success story is the product of sustained funding over decades, helping inform a detailed understanding of underlying tumor biology that in turn translates into new treatments.

Brain tumor research is not at this advanced stage of investment or understanding and the cumulative research-spend on brain tumors in the UK between 2002 and 2011 was less than 1%, and in 2014 only 1.5% of all research-spend by the NCRI (www.ncri.org.uk). The rarity of brain tumor compared to breast cancer and leukaemia is no doubt a factor that contributes to the lower levels of funding. Compounding this under-funding, brain tumors benefit very little from advances elsewhere in “general cancer research” since brain tumors are very different from other cancers. In particular the blood-brain barrier makes it more difficult for novel treatments, developed for systemic cancers, to reach the tumor at therapeutic concentrations. Encouragingly, brain tumors have been identified as a cancer of unmet need and prioritized for research funding, such that CRUK would like to see a 2-3 fold increase in spend over the next 5 years¹³. Whilst increased investment in research does not come with guarantees of lowering mortality, the more we understand these complex cancers and invest in research infrastructure, the greater chances we will have to treat them effectively over the ensuing decades, adding both years to life and life to years of the affected patients and their families. In addition it is essential to engage with initiatives to promote international collaborative working that can usefully pool resources and expertise – especially for the rarer subtypes of brain tumors. Examples include the International Rare Cancers Initiative (IRCI)¹⁴ and the European rare cancer network (EUROCAN).¹⁵

Brain tumor research priorities

A key part of developing a strategy is having a shared perspective on the priorities for research. The James Lind Alliance (JLA) is funded through the NIHR and aims to address uncertainties about the effects of treatment. It achieves this by bringing together patients, carers and clinicians to agree which clinical areas matter most and deserve priority attention. In 2015, the JLA Neuro-Oncology Priority Setting Partnership identified 10 clinical areas in brain and spinal cord tumors on which the research community should focus (table 1) ¹⁶. They cover all aspects of the patient journey from lifestyle factors, early diagnosis, surgery, radiotherapy, disease monitoring, molecular genetics, imaging, quality of life and symptom burden. Most of the JLA priorities are focused on primary brain tumors, however some also map onto brain metastases. Many of these map onto NHS service provision and clinical studies, which fall within the remit of the brain CSG. The JLA top 10 priority questions provide a valuable benchmark and a useful framework for developing a research strategy, however the development of new clinical studies should not be restricted to these priorities alone. Nevertheless the clinical importance of these research priorities are exemplified as follows.

JLA priority 3: *Early diagnosis of brain tumors*

Symptoms of a developing brain tumor can be non-specific, and the average general practitioner (GP) will see few patients who are diagnosed with a brain tumor during the course of their career. In the UK in 2013, 38 % of brain tumor patients visited their GP more than 5 times before diagnosis ¹⁷. Indeed 62% of all brain cancers are only discovered following presentations via Accident and Emergency departments, even where the same patient often previously presented to their GP. This delay in diagnosis increases patient anxiety, and may impact on treatment options and outcome. Timely diagnosis of brain

tumors remains a challenge. The ambition is that earlier diagnosis will identify tumors at a smaller size which might be more amenable to complete surgical resection, in turn leading to a better outcome and prognosis ¹⁸.

JLA priority 6: *Molecular subtyping of tumors*

The advent of The Cancer Genome Atlas (TCGA) heralded a revolution in our molecular understanding of brain tumors. In May 2016 the World Health Organization (WHO) published a revision of the 2007 classification of brain tumors ¹⁹ advising an integrated diagnosis combining molecular and genetic information of tumors with morphology in the classification process ²⁰. A precise molecular diagnosis impacts on both research and routine clinical decision making, facilitating clinical and translational research by allowing better stratification of patients based on the underlying biology of an individual's tumor. It is envisaged this will facilitate the recruitment of more homogenous populations into clinical trials and support a pharmacogenomics exploration of datasets to create novel drug repositioning opportunities. Genome-wide screening at tumor progression/recurrence on tissue or liquid biopsies could facilitate patient reallocation in basket trials. However, at the interface of research and clinical service delivery, one of the challenges is getting the appropriate test results within a clinically meaningful timeframe.

Challenges to addressing the research priorities

The brain tumor research community in the UK is small. There are very few research-leading oncologists, neuroradiologists and neurologists, and only a modest number of brain tumor researchers in neurosurgery and neuropathology. This has an impact on the breadth of leadership within the field, the ability to provide mentorship to aspiring researchers and also the number of clinical studies that can be developed and delivered on to the NCRI portfolio for patients to access. Despite these challenges, in the UK all patients are

treated within the NHS with good contribution to national clinical data sets, such as HES (Hospital Episode Statistics) and the Cancer Registries.

The current infrastructure to develop a clinical study relies heavily on individual university academics or research-active NHS clinicians to develop a research question into a short proposal for review by the CSG and relevant subgroups. That individual will make use of their local network of collaborators that may include a clinical trials unit lacking experience of brain tumor trials. This model is fundamentally flawed and relies heavily on a single motivated individual to navigate the complexities and nuances of grant applications, clinical trial development and protocol writing. Failure is more often because of limited experience with the process, time pressures, or limited supportive infrastructure, rather than the lack of a good idea.

In contrast, the pharmaceutical industry and European Organization for Research and Treatment of Cancer (EORTC) have access to infrastructure and expertise, but their trials will often only open in the UK in a few pre-selected centers - typically the same 5 or 6 units for each successive trial. This inevitably leads to geographic variation in access to new trial drugs for patients. In addition, the pharmaceutical industry does not prioritize brain cancer for new drug development, due to the challenges of delivering trials in this small but diverse group of patients and the issue of drug delivery across the blood-brain barrier. The research community persists in this approach in order to access novel agents and derive marginal but meaningful gains in prognosis and outcome, but it is worthy to note that within the UK, medical oncologists, who tend to have dedicated research time and with whom the pharmaceutical industry often have most links, have not routinely been involved in brain tumor patient management. This stems from the UK's dual training of clinical oncologists in both systemic and radiation therapy and from the historical lack of effective systemic agents. However, with a growing focus on tailored, individualized therapy in all cancer groups, the

lack of medical oncology involvement risks missing opportunities and cross-cutting expertise which might present themselves via early phase units and other connections. It is of note that most of the recent phase III trials in gliomas, whilst negative in terms of improving survival, have been from industry or the EORTC and the lead investigator has been a medical oncologist or neurologists²¹⁻²³.

A strategy for brain tumor research in the UK

The UK neuro-oncology research community is striving towards the dual goals of prevention or cure of brain tumors, and also that people living with and beyond a brain tumor should have the best quality of life possible. At present neither of these ambitions are remotely met. A strategy is needed that can encompass and harness the potential of the community as it works towards improving the diagnosis, treatment, prognosis, and supportive care of patients with brain tumors.

1. Strengthen the existing brain tumor research network

Following publication of the ‘Neuro-Oncology JLA Top Ten’ (table 1), the stakeholders and funders involved in that process developed a strategy to improve the success of funding applications for clinical research and clinical trials. This strategy includes collaborative multi-center research, the support of Clinical Trials Units and the NIHR Research Design Service, and early involvement of public and patient involvement through the use of focused ‘Incubator Days’ (<http://www.neuro-oncology.org.uk/>). Over the last 1-2 years incubator days have been held to develop clinical trials to address epilepsy in glioma and the use of diet in gliomas. As a result the existing network of clinical researchers has been expanded and an application has been submitted to NIHR for the SPRING trial (Seizure PRophylaxis IN Glioma). Whilst this networked approach is more likely to generate successful clinical trials grant applications, it relies heavily on existing networks and

collaborators. The neurosurgical community has established a tumor section of the SBNS to promote research that will enable early career surgeons to develop their ideas. A similar network, the British Neurosurgical Trainee Research Collaborative (BNTRC), exists for trainees to develop their ideas with established links to academic neurosurgeons across the UK and is successfully running a study on long-term survivors with glioblastoma. In a similar fashion the annual Glioma Club meeting provides a forum to foster interactions and networking between scientists and clinicians in the field.

Although the British Neuro-Oncology Society (BNOS) hosts an annual conference to provides a forum for scientists to interact with clinicians treating brain tumor patients, it is poorly attended by clinical oncologists or pediatric oncologists – for whom brain tumors may account for only a proportion of their overall clinical practice. As such, clinical and pediatric oncologists are more likely to attend either more general cancer conferences or conferences targeted towards pediatric malignancies respectively, for research updates. This has inevitably resulted in a poor network. However in September 2016, Addenbrooke's Hospital hosted a 2-day 'bootcamp' that brought together clinical oncologists treating brain tumor patients from across the UK. A follow-up 'CNS bootcamp' is planned for 2017 to develop new clinical trials.

2. Improve access to tissue and imaging

The limited impact of brain cancer research worldwide on clinical outcomes for patients is multifactorial. Central amongst these factors is a fundamental lack of understanding of brain cancer biology. Rectifying this requires more dedicated research focused on brain tumors. A key priority, then, must be to invest more in fundamental research that will generate novel, rational therapies based on a clearer understanding of the biology of these tumors. This idea is gaining momentum in the UK but it will take many

years for the clinical benefit to be realized. Parallel investment in translational research and infrastructure is equally important to optimize the use of currently available drugs and technologies and to accelerate innovation into the clinic. Recent research has identified specific molecular biomarkers for brain cancer and research is urgently required to optimize their use to guide clinical management in the NHS. Imaging advances in humans and pre-clinical models can augment early phase drug development through mechanistic studies linked to tissue-derived data and measurement of novel agent distribution and CNS penetration *in vivo*, in addition to providing early markers of therapeutic response in both early and later phase studies. Whilst the 100,000 Genome project will provide further insight into improving diagnosis, prognosis and personalized treatment of glioma ²⁴, the real cornerstone to improving the understanding of brain tumor biology is to enable access to fully annotated tissue samples enriched with clinical, imaging and outcome data.

Brain Tumor Biobank

Although biobanking is routine for most pediatric brain tumors, only around 30% of adult patients are asked about gifting tumor tissue for research and patients are often not aware that tissue surplus to diagnostic requirements could be used for future research. Healthcare professionals meanwhile are uncertain about the best time and method to broach the subject of tissue donation, and often the discussion does not take place ⁷. Furthermore, there is wide variation across the UK in the resources allocated for tissue biobanking. BRAIN UK ²⁵ is a network of pathology laboratories and 28 of 29 UK neuroscience centers have made their diagnostic and autopsy archives available to researchers. Nevertheless, more funding is needed to improve adult biobanking infrastructure to include frozen tissue samples, primary patient-derived tumor cells and liquid biopsies to create an essential resource to support leading research into disease biology that will have an impact on treatment and care. Crucially, the biological material and molecular annotation must be

supplemented with verified clinical data on symptoms, treatments and outcomes. Investment is needed to develop the data infrastructure and regulatory framework that will allow this to happen on a routine basis. In tandem, a standard minimum imaging protocol should be developed and implemented so that every patient in every unit has the same MRI acquisition.

A national biobank initiative is being developed to provide these valuable resources for laboratory and translational researchers. Support is essential to maximize sample collection by neurosurgeons (e.g. technician support in the operating room) as well as cataloging in the neuropathology department. The full complement of tissue, imaging and clinical data is invaluable to researchers, and access to samples will be based purely on the scientific quality of the application and the proposed exit strategy of the research, as assessed by external peer reviewers - so called scientific meritocracy.

3. Developing capacity

The UK clinical brain tumor research community must develop capacity in order to more effectively deliver clinical studies, through investment in both people and infrastructure. There should be a move away from the traditional split of University ‘academics’ and NHS (non-academic) clinicians, and instead to focus on clinical research teams that can effectively deliver successful grant applications and clinical trials.

People and infrastructure

The multi-disciplinary nature of the management of brain tumors mandates that wider engagement of the clinical neuro-oncology community is essential in order to identify future sustainable leadership. More needs to be done to develop specialist clinical training in the UK through engagement with the Royal Colleges and specialist organizations. Positive examples are the development of sub-specialist neurosurgical oncology by the SBNS and the

Association of British Neurologists Neuro-Oncology Advisory Group. Within neuropathology, training in molecular pathology is to be implemented in the postgraduate curriculum – a positive step towards integrating molecular genetics into routine NHS practice, and a byproduct of which is likely to be research-active individuals. Clinical neuro-oncology imaging forms part of the Royal College of Radiologists core curriculum for higher specialist/ Neuroradiology training, although exposure to advanced quantitative imaging techniques is inconsistent across neuroscience centers. The latter is being addressed through training days recently instituted through the British Society of Neuroradiologists (BSNR), however small numbers of trainees undertaking higher degrees towards clinical academic careers and clinical pressures in NHS posts limits research activity in imaging.

Dedicated fellowships for senior trainees that provide a broad exposure to both oncology and neurology could be considered. Efforts to promote neuro-oncology as a positive career for both clinical and medical oncology need to be developed and greater engagement by neurologists should be promoted. Indeed many of the functional consequences of brain cancer and its treatment highlighted by patients are neurological (e.g. seizures, fatigue, language disturbance and cognitive changes) and more neurologists with an interest in brain cancer are required. Education in clinical trial development and implementation, through fellowships or a higher degree will help ensure that future neuro-oncology leaders will have the skills, contacts and networks to deliver well designed clinical trials.

A further point to consider is that in most other developed countries, once they have completed surgery and radiotherapy, adult brain cancer patients are managed by medical oncologists/neurologists. Brain cancer is a fundamental component of pediatric oncology training, but is not currently part of medical oncology training, but this group of clinicians could deliver future drug trials as part of a wider research community. Indeed early-phase

trials in neuro-oncology are especially challenging and greater investment is required to develop a core number of units able to support brain cancer research with expertise on novel trial designs, in tandem with developing a cadre of research leading clinical and medical oncologists.

Recruiting patients with brain cancer into clinical studies can be challenging therefore no single center will be able to deliver a suitably powered clinical trial. Several clinical trials unit have experience of coordinating and delivering large multi-center brain cancer studies (e.g. Liverpool, Glasgow and University College London) and this network should be exploited and extended for future trials from the initial trial concept. The expertise provided in trial methodology and health economics is invaluable for submitting competitive grants and ultimately delivering trials for patients onto the research portfolio.

The Role of the Brain CSG

The NCRI Brain CSG overarching strategic aim is to support adult brain tumor research through outreach and stakeholder engagement, promoting capacity development and training, developing data and tissue collection and prioritizing clinical research throughout the patient journey. To implement the strategy the following are proposed:

- Re-organization of the brain CSG subgroups: (i) the Glioma subgroup, (ii) the Meningioma, Metastases and others tumors subgroup and (iii) the Survivorship subgroup. Changing the subgroup focus will facilitate a more disease-orientated approach and establish a clear framework for clinicians and researchers to discuss and develop their study and trial ideas

- Complete a scoping exercise of clinical, imaging and laboratory research interests across the UK to identify strengths, weakness and existing collaborations with a view to strengthening the existing networks
- Build the profile of the group through regular engagement with the neuro-oncology community using existing networks. These networks include the ABN and SBNS academic networks and newly formed tumor section, British Neurosurgical Trainees Research Collaborative (BNTRC), British Neuropathology Society (BNS), British Society of Neuroradiologists (BSNR), CNS Bootcamp, Glioma Club, British Neuro-Oncology Society (BNOS) and BRAIN UK, and at annual conference meetings
- Through engagement activities provide mentorship to early-career clinicians with study ideas that can be developed via the CSG subgroups and that will encourage individuals to join the subgroups, which will aid with succession planning when members reach their term on the main group
- Map the CSG strategy to the forthcoming CRUK strategic review for brain tumor research key priorities
- Ensure that the quality of research applications are internationally competitive prior to submission to funding organizations

Conclusions

Brain tumor research in the UK has increased over the last 10-15 years, but a formal, cohesive national strategic direction has been lacking. In order to realize improvements in treatment and prognosis for patients with brain tumors we need to work collaboratively. Being a comparatively small academic community can be an advantage, and we should exploit this. Greater emphasis needs to be placed on co-leadership of research initiatives by a

scientist and a clinician working together. This would allow scientists to optimize benefit from material and data generated in clinical studies and allow clinicians to ensure NHS practice is conducted in a research-supportive manner. National biobanking initiatives are essential to provide high quality clinically annotated samples, linked to national cancer registries that will drive translational research for new drug discovery. Finally we must identify those future leaders, both clinical and laboratory based who can build on the proposed strategy and further develop international collaborative research networks.

Table 1

James Lind Alliance Neuro-Oncology priority questions for research

Research Priority	
1	Do lifestyle factors (e.g. sleep, stress, diet) influence tumour growth in people with a brain or spinal cord tumour?
2	What is the effect on prognosis of interval scanning to detect tumour recurrence, compared with scanning on symptomatic recurrence, in people with a brain tumour?
3	Does earlier diagnosis improve outcomes, compared to standard diagnosis times, in people with a brain or spinal cord tumour?
4	In second recurrence glioblastoma, what is the effect of further treatment on survival and quality of life, compared with best supportive care?
5	Does earlier referral to specialist palliative care services at diagnosis improve quality of life and survival in people with a brain or spinal cord tumours?
6	Do molecular subtyping techniques improve treatment selection, prediction and prognostication in people with a brain or spinal cord tumour?
7	What are the long-term physical and cognitive effects of surgery and/or radiotherapy when treating people with a brain or spinal cord tumour?
8	What is the effect of interventions to help carers cope with changes that occur in people with a brain or spinal cord tumour, compared with standard care?
9	What is the effect of additional strategies for managing fatigue , compared with standard care, in people with a brain or spinal cord tumour?
10	What is the effect of extent of resection on survival in people with a suspected glioma of the brain or spinal cord?

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